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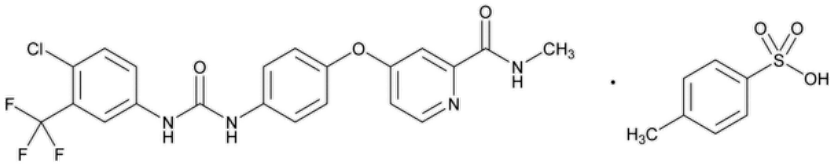
Add the following:

▲Sorafenib Tosylate



$C_{21}H_{16}ClF_3N_4O_3 \cdot C_7H_8O_3S$ 637.03

2-Pyridinecarboxamide, 4-[4-[[[[4-chloro-3-(trifluoromethyl)phenyl]amino]carbonyl]amino]phenoxy]-*N*-methyl-, mono(4-methylbenzenesulfonate); 4-(4-{3-[4-Chloro-3-(trifluoromethyl)phenyl]ureido}phenoxy)-N^2-methylpyridine-2-carboxamide mono(4-methylbenzenesulfonate) CAS RN®: 475207-59-1.

Sorafenib (free base)

$C_{21}H_{16}ClF_3N_4O_3$ 464.83 CAS RN®: 284461-73-0.

DEFINITION

Sorafenib Tosylate contains NLT 97.0% and NMT 102.0% of sorafenib tosylate ($C_{21}H_{16}ClF_3N_4O_3 \cdot C_7H_8O_3S$), calculated on the anhydrous and solvent-free basis.

IDENTIFICATION

• **A. Spectroscopic Identification Tests ⟨197⟩, *Infrared Spectroscopy*:** [Note—Methods described in 197K or 197A may be used.]

• **B.** The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.

ASSAY

• **Procedure**

Protect solutions containing sorafenib tosylate from light. Do not sonicate.

Solution A: 1 mL of phosphoric acid and 1 g of potassium phosphate, monobasic in 1 L of water

Solution B: Absolute alcohol and acetonitrile (4:6)

Mobile phase: See *Table 1*. Return to original conditions, and equilibrate the system for 10 min.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	95	5
2	95	5
24	56.5	43.5
32	10	90
37	10	90

Diluent: Dimethyl sulfoxide, acetonitrile, and phosphoric acid (85:15:0.1)

Standard solution: 1.0 mg/mL of USP Sorafenib Tosylate RS in *Diluent*

Sample solution: 1.0 mg/mL of Sorafenib Tosylate in *Diluent*

Chromatographic system

(See *Chromatography ⟨621⟩, System Suitability*.)

Mode: LC

Detector: UV 235 nm

Column: 2.1-mm × 15-cm; 3.5-µm packing L7

Column temperature: 75°

Flow rate: 0.6 mL/min

Injection volume: 3 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 1.6

Relative standard deviation: NMT 0.73%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of sorafenib tosylate ($C_{21}H_{16}ClF_3N_4O_3 \cdot C_7H_8O_3S$) in the portion of Sorafenib Tosylate taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

r_U = peak response from the *Sample solution*

r_S = peak response from the *Standard solution*

C_S = concentration of USP Sorafenib Tosylate RS in the *Standard solution* (mg/mL)

C_U = concentration of Sorafenib Tosylate in the *Sample solution* (mg/mL)

Acceptance criteria: 97.0%–102.0% on the anhydrous and solvent-free basis

IMPURITIES

• **Organic Impurities**

Protect solutions containing sorafenib tosylate from light. Do not sonicate.

Solution A, Solution B, Mobile phase, Diluent, Standard solution, and **Sample solution:** Prepare as directed in the *Assay*.

System suitability solution: 3.0 µg/mL of USP Sorafenib Related Compound H RS in *Standard solution*. It contains 3.0 µg/mL of USP Sorafenib Related Compound H RS and 1.0 mg/mL of USP Sorafenib Tosylate RS in *Diluent*.

Sensitivity solution: 0.5 µg/mL of USP Sorafenib Tosylate RS in *Diluent*, from *Standard solution*

Chromatographic system

(See *Chromatography ⟨621⟩, System Suitability*.)

Mode: LC

Detector: UV 235 nm

Column: 2.1-mm × 15-cm; 3.5-µm packing L7

Column temperature: 75°

Flow rate: 0.6 mL/min

Injection volume: 3 µL

System suitability

Samples: *System suitability solution* and *Sensitivity solution*

Suitability requirements

Resolution: NLT 2.2 between the sorafenib related compound H and sorafenib peaks, *System suitability solution*

Signal-to-noise ratio: NLT 10, *Sensitivity solution*

Analysis

Sample: *Sample solution*

Calculate the percentage of each impurity in the portion of Sorafenib Tosylate taken:

$$\text{Result} = [r_U \times (1/F)]/\{\Sigma[r_U \times (1/F)] + r_S\} \times 100$$

r_U = peak response of each impurity from the *Sample solution*

F = relative response factor (see *Table 2*)

r_S = peak response of sorafenib from the *Sample solution*

Acceptance criteria: See *Table 2*. The reporting threshold is 0.05%. Disregard toluenesulphonic acid at a relative retention time of 0.07. [NOTE—Toluenesulphonic acid is the counter ion of sorafenib and is present in the chromatogram of the *Sample solution*.]

Table 2

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Sorafenib impurity A[a]	0.15	1.5	0.15
Sorafenib impurity B[b]	0.33	2.0	0.15
Sorafenib impurity C[c]	0.68	0.80	0.15
Sorafenib impurity D[d]	0.69	2.2	0.15
Sorafenib impurity E[e]	0.73	1.5	0.15
Sorafenib impurity F[f]	0.92	1.1	0.15
Sorafenib related compound H	0.98	1.1	0.30
Sorafenib	1.00	—	—
Any individual unspecified impurity	—	1.0	0.10
Total impurities	—	—	1.0

[a] 4-(4-Aminophenoxy)-*N*-methylpicolinamide.

[b] 4-(4-Formamidophenoxy)-*N*-methylpicolinamide.

[c] 4-Chloro-3-(trifluoromethyl)aniline.

[d] Isopropyl {4-[2-(methylcarbamoyl)pyridin-4-yl]oxyphenyl}carbamate.

[e] *N*,*N*′-Bis{4-[2-(*N*-methylcarbamoyl)-4-pyridyloxy]phenyl}urea.

[f] *N*-Methyl-4-{4-[3-(3-trifluoromethylphenyl)ureido]phenoxy}picolinamide.

SPECIFIC TESTS

• **WATER DETERMINATION ⟨921⟩, *Method I***

Sample: 200 mg

Analysis: Evaporation technique

Temperature: 150°

Heating time: 3 min

Carrier gas: Nitrogen

Flow rate: 70 mL/min

Reagent: Hydranal Coulomat AG, or Hydranal Coulomat AK or equivalent

Acceptance criteria: NMT 1.0%

ADDITIONAL REQUIREMENTS

• **PACKAGING AND STORAGE:** Preserve in tight containers, and protect from light. Store at room temperature.

• **USP REFERENCE STANDARDS ⟨11⟩**

USP Sorafenib Tosylate RS

USP Sorafenib Related Compound H RS

4-(4-{3-[2-Chloro-3-(trifluoromethyl)phenyl]ureido}phenoxy)-*N*-methylpicolinamide.

$C_{21}H_{16}ClF_3N_4O_3$ 464.83▲ (USP 1-May-2021)

Auxiliary Information - Please check for your question in the FAQs before contacting USP.

Topic/Question	Contact	Expert Committee
SORAFENIB TOSYLATE	Documentary Standards Support	SM32020 Small Molecules 3
REFERENCE STANDARD SUPPORT	RS Technical Services RSTECH@usp.org	SM32020 Small Molecules 3

Chromatographic Database Information: Chromatographic Database

Most Recently Appeared In:
Pharmacopeial Forum: Volume No. 49(3)

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